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Development of end stage renal disease following an acute cardiac event

Tammy M. Keough-Ryan[1], Bryce A. Kiberd[1], Jafna L. Cox[1], Kara J. Thompson[1] and Catherine M. Clase[2,3]

[1]*Department of Medicine, Dalhousie University, Halifax, Nova Scotia, Canada;* [2]*Department of Medicine, McMaster University, Hamilton, Ontario, Canada and* [3]*Clinical Epidemiology and Biostatistics, McMaster University, Hamilton, Ontario, Canada*

We determined the rate and risk factors for end-stage renal disease (ESRD) in consecutive patients discharged after a cardiac event in a large, unbiased Canadian cohort that receives universal health coverage. A total of 8236 adults hospitalized over a 2 year period were followed for up to 7.5 years and the incidence of ESRD and mortality determined. Of these, 113 reached ESRD (stage 5). Patients with moderate (stage 3) and severe (stage 4) renal insufficiency were more likely to develop ESRD than those patients at stage 1 or 2. However, patients with moderate renal insufficiency were 78.6 times more likely to die than to develop ESRD. Absolute rates of progression to ESRD per 100-patient years were 0.08 at stages 1 and 2, 0.17 at stage 3 and 4.27 at stage 4. Age, diabetes, hypertension and congestive heart failure also predicted ESRD. We found that patients with stage 4 disease are at high risk of ESRD after a cardiac admission while those at stage 3 are far more likely to die than to develop ESRD.

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Correspondence: *Tammy M. Keough-Ryan, Department of Medicine, Dalhousie University, Room 5097 Dickson Building, 5820 University Avenue, Halifax, Nova Scotia, Canada B3H 1V8.*
E-mail: tammy.keough-ryan@cdha.nshealth.ca

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Kidney disease and cardiovascular disease are closely linked. Patients with chronic renal insufficiency (CRI) have a high burden of cardiovascular disease, and in many studies CRI is an independent risk factor for cardiovascular disease.[1] In addition to being a risk factor for atherosclerosis, CRI is a predictor of increased mortality in patients with congestive heart failure (CHF) and CRI is associated with CHF.[2,3]

Several studies have shown that CRI is prevalent in patients admitted for ischemic heart disease and CHF.[4–9] The subsequent risk of end-stage renal disease (ESRD) in these patients has not been studied extensively. In a retrospective study of Medicare patients in Georgia, McClellan *et al.*[10] described the prevalence of low glomerular filtration rate (GFR) (defined as GFR estimated by the Modification of Diet in Renal Disease GFR equation (MDRD GFR) of less than 60 ml/min/1.73 m^2) as being 52% in patients surviving admission for myocardial infarction (MI) and 60% in survivors of admission for CHF. Over a 3-year follow up, ESRD occurred in 3% of patients with low GFR and MI, and in 6.1% of patients with low GFR and CHF. Unless GFR was low, ESRD was very uncommon in both patients with MI and CHF (1 of 498 patients). Multivariable analysis of risks for ESRD was precluded in this data set by the relatively limited number of patients who developed ESRD (32 events). In this study, it was not known whether patients had been assessed by a nephrology sub-specialist either before or after their index admission.

We primarily studied the rate of ESRD in consecutive patients discharged after a cardiac event in a large, unbiased Canadian cohort that receiving universal health coverage. We secondarily studied the prevalence of renal insufficiency, the multivariable risk factors for ESRD, the rate of ESRD relative to the rate of death, the measurement properties of MDRD GFR, serum creatinine, the measurement properties of MDRD GFR and serum creatinine in predicting ESRD, the proportion of patients known by nephrologists before the admission, and the association of nephrology consultation with ESRD.

RESULTS

We identified 15,237 unique patients in the database; 9961 had discharge diagnoses of acute coronary syndrome (ACS), CHF, or both. We excluded patients from the analysis for the

following reasons: other diagnoses ($n=5276$), serum creatinine level absent ($n=737$), less than 40 μmol/l ($n=19$), or greater than 1000 μmol/l ($n=7$), on renal replacement therapy prior to admission ($n=56$), requiring renal replacement therapy during the index admission ($n=13$), died during the index admission ($n=887$), and/or unclassifiable with respect to ESRD ($n=6$). We included 8,236 patients in the final analysis with discharge diagnoses: ACS ($n=4979$), CHF ($n=2656$), and CHF and ACS ($n=601$).

Participants excluded on the basis of missing serum creatinine did not differ by age, sex, diabetes, or discharge diagnosis from those included (data not shown). Demographics of the whole study group and the three diagnostic categories are shown in Table 1.

Over the 4.4- to 7.5-year follow-up period, 113 patients developed ESRD, a cumulative incidence of 1.4%. Figure 1a shows that patients with diagnosis of CHF, with or without ACS, were more likely to develop ESRD than those with diagnosis of ACS alone (log-rank $P<0.0001$ and <0.0001, respectively). Patients with GFR <30 ml/min/1.73 m^2 were more likely to develop ESRD than those with GFR 30–<60 ml/min/1.73 m^2 or GFR $\geqslant 60$ ml/min/1.73 m^2 (Figure 1b) (log-rank $P<0.0001$ and <0.0001, respectively). There was no significant difference between patients with GFR 30–60 ml/min/1.73 m^2 and those with GFR $\geqslant 60$ ml/min/1.73 m^2 ($P=0.0189$) using the predetermined Bonferonni-corrected threshold value of 0.006. The cumulative incidence of ESRD was highest in the subgroup of patients with GFR <15 ml/min/1.73 m^2 (35/110 or 31.8%). Couchoud creatinine cut-off points also identified patients likely to develop ESRD. Patients above the cut-off point corresponding to <30 ml/min/1.73 m^2 were more likely to develop ESRD than those between the 30 and 60 ml/min/1.73 m^2 cut-off points (log-rank $P<0.0001$) and less likely than those $\geqslant 60$ ml/min/1.73 m^2 cut-off point (log-rank $P<0.0001$). There was no statistically significant differences between patients with the 30 and 60 ml/min/1.73 m^2 cut-off points and those with the $\geqslant 60$ ml/min/1.73 m^2 cut-off point (log-rank $P=0.1149$; Figure 1c). Receiver operating characteristic curves showed that serum creatinine level and MDRD GFR were equally good predictors of ESRD (Figure 2). Table 2 shows sensitivity, specificity, and likelihood ratios for prediction of ESRD.

Table 3 shows the crude hazard rates for mortality and ESRD. Patients were far more likely to die than to develop ESRD, except in patients with severely low GFR (GFR <30 ml/min/1.73 m^2).

In the adjusted Cox proportional hazard multivariable analysis, we found a discharge diagnosis of CHF (alone or with ACS), moderate and severely low GFR (by MDRD GFR), diabetes, hypertension, and anemia were independent

Table 1 | Baseline characteristics of study participants

Baseline variables	ACS n=4979 mean (s.d.) n (%)	CHF n=2656 mean (s.d.) n (%)	CHF & ACS n=601 mean (s.d.) n (%)	Full cohort n=8236 mean (s.d.) n (%)
Age (years)	65.2 (13.0)	75.8 (11.1)	76.8 (11.4)	69.2 (13.2)
60–<70 years	1270 (25.5%1)	407 (15.3%)	109 (18.1%)	1786 (21.7%)
70–<80 years	1299 (26.1%)	930 (35.0%)	225 (37.4%)	2454 (29.8%)
⩾80 years	716 (14.4%)	1092 (41.1%)	197 (32.8%)	2005 (24.3%)
Gender (women)	1887 (37.9%)	1415 (53.2%)	291 (48.4%)	3593 (43.6%)
Diabetes	1284 (25.8%)	1050 (39.5%)	293 (48.8%)	2627 (32.9%)
Hypertension	3690 (74.1%)	1822 (68.6%)	447 (74.4%)	5959 (72.4%)
Current smoker	1537 (30.9%)	417 (15.7%)	132 (21.9%)	2086 (25.3%)
Hyperlipidemia	3393 (68.1%)	567 (21.4%)	288 (47.9%)	4248 (51.6%)
GFR (ml/min/1.73 m^2)	68.6 (22.6)	53.0 (22.8)	54.2 (22.8)	62.5 (23.9)
Creatinine (μmol/l)	102 (44)	130 (72)	128 (67.6)	113 (58)
GFR				
>60 ml/min/1.73 m^2	3256 (65.4%)	938 (35.3%)	227 (37.8%)	4421 (53.7%)
30–<60 ml/min/1.73 m^2	1518 (30.5%)	1288 (48.5%)	279 (46.4%)	3085 (37.5%)
<30 ml/min/1.73 m^2	205 (4.1%)	430 (16.2%)	95 (15.8%)	730 (8.9%)
Total cholesterol (mmol/l)	5.2 (1.3)	4.8 (1.4)	4.8 (1.2)	5.2 (1.3)
LDL (mmol/l)	3.2 (1.0)	3.0 (1.1)	3.1 (1.0)	3.2 (1.0)
Hemoglobin (g/l)	139 (17)	127 (21)	130 (21.9)	134 (20)
Hemoglobin				
⩾120 g/l	4396 (88.3%)	1708 (64.3%)	430 (71.6%)	6534 (79.3%)
100–<120 g/l	439 (8.8%)	625 (23.5%)	118 (19.6%)	1182 (14.4%)
<100 g/l	120 (2.4%)	280 (10.5%)	52 (8.7%)	452 (5.5%)
Missing	24 (0.5%)	43 (1.6%)	1 (0.2%)	68 (0.8%)
Previous visit to nephrologist				
Total	190 (3.8%)	156 (5.9%)	50 (8.3%)	396 (4.8%)
Pre event	46 (0.9%)	41 (1.5%)	14 (2.3%)	101 (1.2%)
Post event	144 (2.9%)	115 (4.3%)	36 (6.0%)	295 (3.6%)

ACS, acute coronary syndrome; CHF, congestive heart failure; GFR, glomerular filtration rate; LDL, low-density lipoprotein cholesterol.
Missing values: cholesterol, 4,246 (51.6%) and LDL (4,607), 55.9%.

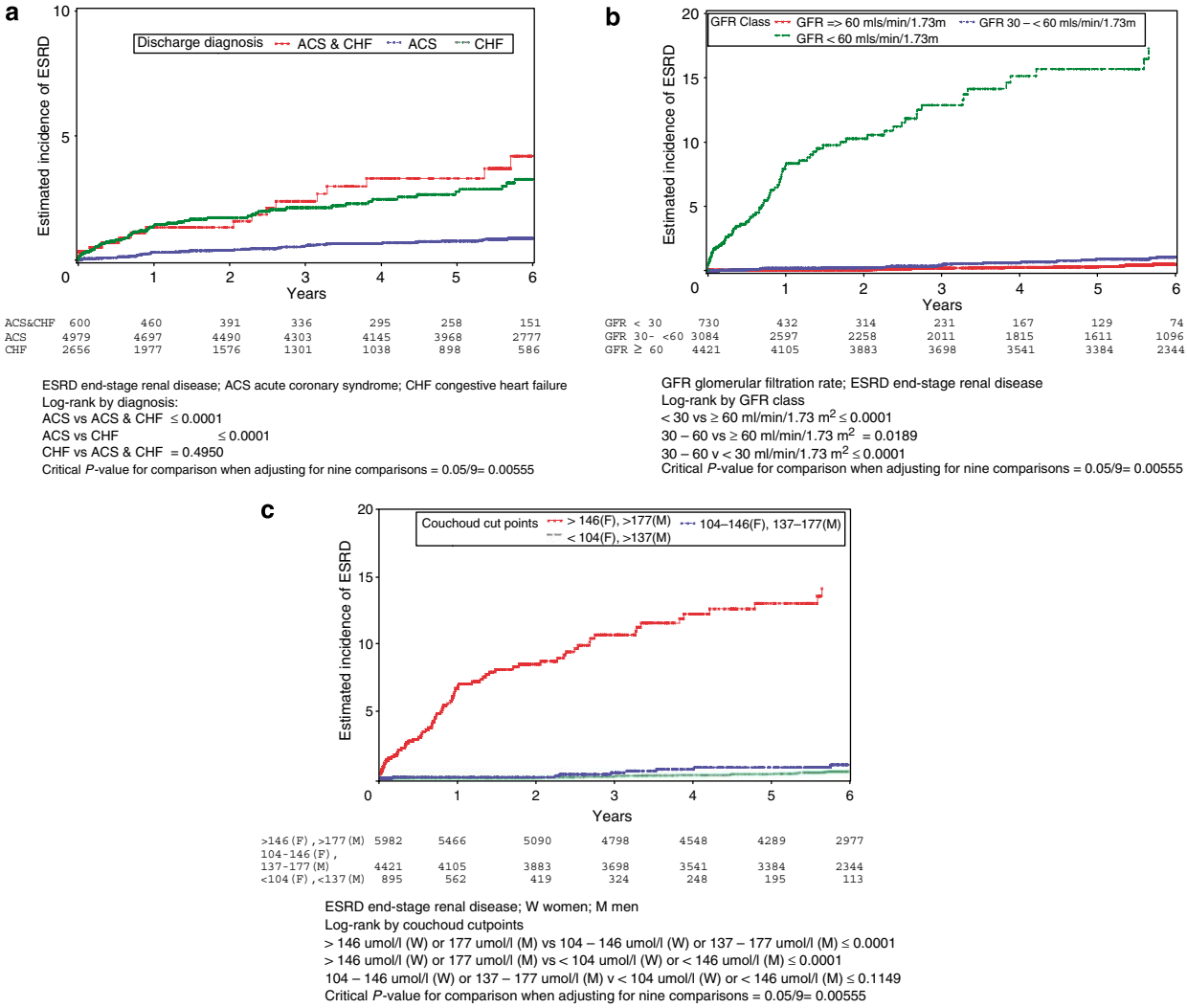


Figure 1 | End stage renal disease incidence. (**a**) Kaplan–Meier plot showing cumulative incidence of ESRD by cardiac diagnosis. (**b**) Kaplan–Meier plot showing cumulative incidence of ESRD by renal function on admission. (**c**) Kaplan–Meier plot showing cumulative incidence of ESRD by creatinine cut-off points.

predictors of the development of ESRD (Table 4). After adjustment for MDRD GFR, women and older patients were found to be less likely to develop ESRD than men or younger patients. After initiation of chronic renal replacement therapy, mortality was determined to be 80% at 4 years.

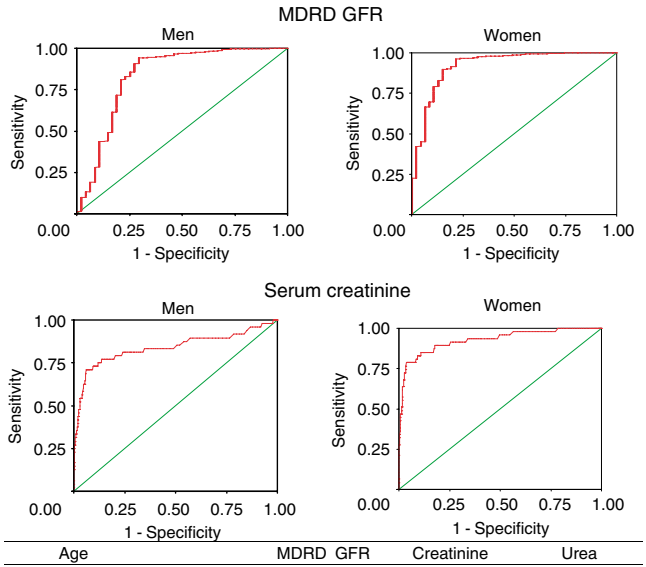
Due to statistical concerns of including too many variables for the number of events, interaction terms for cardiac diagnosis and GFR levels were not incorporated into the final multivariate model. Models that included these terms were terms were run by the author. The results showed that although hazard ratio for ESRD was higher with decreased GFR, the magnitude of risk remained higher with CHF diagnosis. This suggests CHF is an independent predictor of ESRD. Atrial fibrillation was also not included in the multivariate analysis as a co-diagnosis due to the small number of patients with atrial fibrillation who progressed to ESRD (8/113).

We identified, through registry linkage, the following 101 patients who had been assessed by a nephrologist before their cardiac admission: 84 patients (1.0%) within the previous 2 years and a further 17 patients more than 2 years before. This included 25 of the 113 (22.1%) who had developed ESRD. Patients who had been evaluated by a nephrologist, compared with those who had not, were more likely to have diabetes (51.5 vs 31.7%; $P<0.0001$), hypertension (88.1 vs 72.2%; $P=0.0003$), decreased renal function (31.7 vs 62.9 ml/min/1.73 m^2; $P<0.0001$), and lower hemoglobin level (120 vs 136 g/l; $P<0.0001$), and were less likely to be current smokers (9.9 vs; 25.5%; $P=0.0003$). When previous consultation by a nephrologist was included in the Cox model (Table 4), nephrology consultation was associated with increased risk of subsequent ESRD (hazard ratio 4.20; 95% confidence interval 2.49–7.09), and the risks associated with moderate and severely low GFR were attenuated.

DISCUSSION

This study shows that low GFR is prevalent (46.3%) in survivors of admission for ACS or CHF. The development of ESRD (113/8236 or 1.4%) is relatively uncommon at 6 years

of follow-up, except in those patients with GFR < 30 ml/min/1.73 m^2 (72/730 (9.9%) when assessed by MDRD GFR, 77/895 (8.6%)) when assessed by Couchoud cut-off points). At all levels of GFR, these patients are more likely to die than to develop ESRD. ESRD may have been under-reported, particularly in the elderly population, due to censoring (patient or medical decision to pursue conservative management).



Age		MDRD GFR	Creatinine	Urea
Men	0.52	0.84	0.84	0.84
	(0.44,0.60)	(0.76,0.91)	(0.76,0.92)	(0.77,0.91)
Women	0.61	0.92	0.93	0.87
	(0.54,0.67)	(0.88,0.97)	(0.88,0.97)	(0.82,0.93)

Figure 2 | Receiver operating characteristic curves showing measurement properties of MDRD GFR and of serum creatinine at admission as predictors of ESRD within 4.44 years. Measurement properties of age and urea are shown only in a tabulated format.

We have extended the work of McClellan[10] on the risk of ESRD after cardiac discharge by showing that CHF, as compared with ACS, is a multivariable risk factor for ESRD, independent of level of renal function. Rates of ESRD are lower than those observed by McClellan (0.97% per annum after MI in McClellan's data, 0.14% per annum after ACS in our data; 2.07% after CHF in McClellan's data, 0.63 and 0.76% in our data after CHF without and with ACS, respectively). These differences may be explained by the selection of the study group (Medicare patients in McClellan's study, and the inclusive provincial cohort in our study), in the health care systems and policies between the two countries (US and Canada), and, in the case of the ischemic group, from the difference in definition used.

We found that in addition to cardiac discharge diagnosis and renal function, age, diabetes, hypertension, and hemoglobin level also predicted ESRD. It is a limitation of this study that we were unable to include cardiac history and hyperlipidaemia in the analysis because of the large number of missing values for these data items (64 and 54.1% respectively). After adjustment for level of renal function, we found that older patients were less likely to reach ESRD than younger patients, consistent with effects identified in unselected outpatients by others.[11,12] It is likely that the lower ESRD risk in the elderly reflects informative censoring and increased competing risks of death in elderly people. It is also possible that low GFR may not carry the same prognostic value in elderly people as in young people: low GFR in younger people may reflect pathologic processes with a

Table 2 | Sensitivity, specificity, positive, and negative likelihood ratios for < 60 and < 30 ml/min/1.73 m^2 thresholds for Couchoud cut-off points and MDRD GFR–sensitivity/specificity of model with a 4.44-year ESRD event cut-off

Test	ESRD		Test characteristics of cut point			
	Yes	No	Sensitivity (95% CI)	Specificity (95% CI)	LR +ve	LR −ve
Using Couchoud cut-off points						
< 60 ml/min/1.73 m^2[a]						
Yes	81	2172	85.3 (76.8, 91.0)	73.3 (72.3, 74.3)	3.2 (2.9, 3.5)	0.2 (0.1, 0.3)
No	14	5969				
< 30 ml/min/1.73 m^2[b]						
Yes	74	821	77.9 (68.6, 85.1)	89.9 (89.2, 90.6)	7.7 (6.8, 8.8)	0.2 (0.2, 0.4)
No	21	7320				
Using MDRD GFR						
< 60 ml/min/1.73 m^2						
Yes	85	3730	89.5 (81.7, 94.2)	54.2 (53.1, 55.3)	2.0 (1.8, 2.1)	0.2 (0.1, 0.3)
No	10	4411				
< 30 ml/min/1.73 m^2						
Yes	70	660	73.7 (64.0, 73.5)	91.9 (91.3, 92.5)	9.1 (7.9, 10.5)	0.3 (0.2, 0.4)
No	25	7481				
Overall	95	8141				

CI, confidence interval; ESRD, end-stage renal disease (at 4.44-year follow-up); LR −ve, likelihood ratio if negative; LR +ve, likelihood ratio if positive; MDRD GFR, glomerular filtration rate estimated according to the Modification of Diet in Renal Disease equation.
[a]Serum creatinine: > 146 μmol/l (women) or > 177 μmol/l (men).
[b]Serum creatinine: ⩾ 104 μmol/l (women) or ⩾ 137 μmol/l (men).

higher likelihood of progression, whereas in many elderly people low GFR may simply reflect age-related decline.

Diabetes and hypertension are both well-described risk factors for progression of kidney disease.[13,14] Anemia, although a risk factor, may not be a causal link for ESRD development, but is more likely associated with other risk factors for progression such as inflammation, comorbidity, or more advanced renal insufficiency within the GFR class. A recent meta-analysis found no evidence that improving the hemoglobin status with erythropoietin reduced progression of renal failure.[15]

One of the current areas of discussion within nephrology community is how to define and communicate CRI to the non-nephrology community.[16] Consensus guidelines argue that reporting serum creatinine be abandoned in favor of an estimation of GFR based on an accepted formula.[17] Our present analysis shows that Couchoud sex-specific cut-off points of creatinine greater than 146 μmol/l for women or 177 μmol/l (equivalent to a GFR of <30 ml/min/1.73 m^2) are as valid as cut-off points defined by MDRD GFR in defining high risk for progression to ESRD in this patient group. In receiver operating characteristic curves curve analysis, sex-specific serum creatinine performs as well as a predictor of ESRD before death as does MDRD GFR.

Recent studies of elderly patients with diabetes in the general population have compared the risks of death and ESRD stratified by baseline GFR.[11,18–21] These studies showed the risk of death to be greater than the requirement for renal replacement therapy, even for people with low GFR. Keith *et al.*[19], studying a managed care organization, showed mortality/ESRD rate ratios of 17.7, 18.7, and 2.3 for GFR $\geqslant 60$, 30–<60, and <30 ml/min/1.73 m^2, respectively. Go *et al.*[20] studied the members of a similar registry and found high mortality, but low progression of 0.28%, to dialysis treatment and 0.03% to transplant. These rates are

Table 3 | Crude mortality rates and rates of ESRD, stratified by cardiac diagnosis, age and renal function

	Death/100 patient years	ESRD/100 patient years	Death/ESRD
Full cohort	9.34 (8.85, 9.82)	0.29 (0.20, 0.38)	31.99
Cardiac diagnosis			
ACS	4.69 (4.39, 4.99)	0.14 (0.091, 0.20)	32.48
CHF	21.80 (21.00, 22.60)	0.64 (0.48, 0.79)	34.27
CHF and ACS	17.31 (15.76, 18.85)	0.77 (0.41, 1.13)	22.45
Age (years)			
<60	2.11 (1.78, 2.43)	0.27 (0.15, 0.39)	7.80
60–69	5.88 (5.32, 6.44)	0.32 (0.18, 0.45)	18.51
70–79	11.91 (11.25, 12.56)	0.34 (0.22, 0.46)	34.80
$\geqslant 80$	23.10 (22.16, 24.04)	0.21 (0.11, 0.32)	108.72
GFR (ml/min/1.73 m^2)			
>60	5.37 (5.04, 5.71)	0.08 (0.037, 0.12)	67.38
30–<60	13.10 (12.50, 13.71)	0.17 (0.093, 0.24)	78.62
<30	33.45 (31.70, 35.19)	4.27 (3.52, 5.02)	7.83

ACS, acute coronary syndrome; CHF, congestive heart failure; ESRD, end-stage renal disease; GFR, glomerular filtration rate.

Table 4 | Cox proportional hazards model for ESRD, estimating glomerular filtration rate with MDRD GFR, and with Couchoud's cut-off points

	Models using MDRD GFR to estimate GFR category		Models using Couchoud cut-off points to estimate GFR category	
Variable	Hazard ratio 95% CI	Hazard ratio 95% CI	Hazard ratio 95% CI	Hazard ratio 95% CI
Cardiac diagnosis				
ACS	Referent	Referent	Referent	Referent
CHF	1.79 (1.13, 2.82)	1.91 (1.21, 3.02)	1.84 (1.16, 2.90)	1.97 (1.25, 3.12)
CHF and ACS	2.35 (1.30, 4.25)	2.04 (1.12, 3.69)	2.23 (1.22, 4.06)	2.00 (1.10, 3.62)
GFR (ml/min/1.73 m^2)				
>60	Referent	Referent	Referent	Referent
30–<60	2.37 (1.24, 4.50)	1.99 (1.04, 3.79)	1.91 (0.88, 4.156)	1.54 (0.70, 3.36)
<30	35.9 (19.7, 65.6)	25.4 (13.7, 47.3)	23.29 (13.92,38.96))	17.45 (10.28,29.63)
Diabetes	2.87 (1.87, 4.40)	2.78 (1.81, 4.27)	2.69 (1.75, 4.12)	2.58 (1.68, 3.96)
Age (years)				
<60	Referent	Referent	Referent	Referent
60–69	0.66 (0.39, 1.12)	0.97 (0.57, 1.67)	0.67 (0.40, 1.13)	1.01 (0.59, 1.72)
70–79	0.44 (0.26, 0.75)	0.68 (0.40, 1.18)	0.41 (0.24, 0.68)	0.66 (0.38, 1.13)
$\geqslant 80$	0.18 (0.09, 0.36)	0.28 (0.14, 0.57)	0.18 (0.09, 0.35)	0.28 (0.14, 0.57)
Women	0.64 (0.45, 0.95)	0.69 (0.46, 1.0)	0.74 (0.51, 1.10)	0.78 (0.53, 1.16)
Hypertension	3.02 (1.56, 5.82)	2.71 (1.40, 5.24)	2.93 (1.52, 5.64)	2.60 (1.34, 5.03)
Smoker current	1.46 (0.92, 2.34)	1.74 (1.10, 2.78)	1.36 (0.86, 2.17)	1.66 (1.05,2.64)
Hemoglobin				
>120 g/l	Referent	Referent	Referent	Referent
100–<120 g/l	1.75 (1.06, 2.88)	1.61 (0.98, 2.64)	1.91 (1.16, 3.13)	1.70 (1.04, 2.78)
<100 g/l	3.95 (2.37, 6.60)	4.00 (2.39, 6.67)	4.50 (2.71, 7.48)	4.40 (2.64, 7.33)
Nephrology visit pre admission	Not included	4.20 (2.49, 7.09)	Not included	4.95 (2.95, 8.29)

ACS, acute coronary syndrome; CHF, congestive heart failure; ESRD, end-stage renal disease; MDRD GFR glomerular filtration rate estimated using the modification of diet in renal disease equation.

lower than that in our participants (Table 3), who were at higher mortality risk on account of their recent hospitalization for a cardiac event. Similarly, two large population-based studies have shown a higher rate of development of vascular disease and death rather than ESRD.[21,22]

Several groups have conducted *post hoc* analysis of the antihypertensive and lipid lowering treatment to prevent heart attack trial and showed high rates of cardiovascular events and low rates of ESRD.[23–25] The impact of death was underestimated in our study, as death in hospital was excluded. A re-analysis of our data with the inception time point at the day of admission rather than discharge, shows relative rates of death to ESRD of 96, 92, and 10 for GFR $\geqslant$60, GFR 30–$<$60, and $<$30 ml/min/1.73 m^2, respectively.

We found that very few patients, 2.4% of those with low GFR and 7.7% of those with GFR less than 30 ml/min/1.73 m^2, had been assessed by a nephrologist before cardiac admission. Patel *et al.*[18] similarly reported a low rate of assessment of patients with severe CRI by nephrology subspecialists in a cohort of elderly patients. Our data, however, suggest that the use of nephrology consultation may have been carefully selective: the finding of a positive association between nephrology visit and ESRD is likely due to the referral of those with more progressive disease. This hypothesis is supported by the finding of higher prevalence of the risk markers diabetes and hypertension, and by the lower GFRs and lower hemoglobin levels observed in those referred compared with those who were not (The alternative hypothesis that nephrology referral is harmful cannot be excluded, but seems unlikely).

We have shown that patients discharged from hospital following cardiac events, who have low GFR, are at high risk of death, and that this increases in a stepwise manner at lower levels of GFR. However, in univariate analysis, we were unable to show a difference between patients with GFR 30–$<$60 ml/min/1.73 m^2 and those with GFR $\geqslant$60 ml/min/1.73 m^2 with respect to risk of progression to ESRD. In multivariable analysis, the hazard ratio for ESRD in patients with MDRD GFR 30–$<$60 ml/min/1.73 m^2 is 2.37 (95% confidence interval 1.24–4.50), compared with 35.9 (95% confidence interval 19.7–65.6) for those with GFR $<$30 ml/min/1.73 m^2. These results are congruent with those of Hallan *et al.*[21] who followed 65,604 participants in a population-based health survey in Nord-Tondelag County, Norway, and found that although 20% of those with GFR less than 30 ml/min/1.73 m^2 progressed to ESRD over the subsequent 8 years, ESRD occurred in only 2 and 1% of those with GFR 30–45 and 45–60 ml/min/1.73 m^2, respectively.

In our participants with GFR 30–$<$60 ml/min/1.73 m^2, death was 79 times more likely than ESRD. The lower rates of ESRD are likely the result of competing risk of death. Since no specific nephrologic interventions have been shown to decrease the risk of death, our data support selective, rather than universal, nephrology consultation for people with GFR in this range. Their optimal investigation and management warrants further research. Given that these patients have had a cardiovascular event, they are at increased risk of subsequent events and mortality. They should receive maximal cardiovascular risk reduction therapy regardless of CRI status.[26–28] We have previously reported that therapy is often less intense post cardiac event in those with CRI.[4]

Patients discharged following a cardiac event, whose GFR is $<$30 ml/min/1.73 m^2, experience a different prognosis: 33.5% annual mortality, 4.3% annual risk of ESRD, and a much lower ratio of death to ESRD of 7.8. Similarly, in the general population, using more extreme cut-off points for creatinine of $>$300 μmol/l in men and $>$250 μmol/l in women, Evans *et al.*[12] identified a group with 80% progression to ESRD over 6 years. The likelihood that these patients will benefit from the scarce resource of nephrology consultation is much higher.

Our study has several limitations. This was an observational study; while the findings may indicate associations, they cannot establish causal relationships. We assigned a renal function group based on a single serum creatinine level on admission without knowledge of prior or follow-up values. Patients who left the province or had events out of province may not have been included; therefore, this analysis may have underestimated actual events.

We may have underestimated the proportion of patients assessed by nephrology sub-specialists: some patients could have been seen earlier than our linkage date, and some may have been seen by internists with expertise in nephrology who work in rural communities. We do not know the reasons for referral and risk factors at the time of referral. We did not have information on proteinuria and the rate of change of GFR, both of which are likely to be important predictors of ESRD.

In summary, clinically important risk factors for development of ESRD in patients admitted for a cardiac event are easily identifiable. Rates of progression to ESRD in people with GFR 30–$<$60 ml/min/1.73 m^2 in the medium term are low. High competing risks of death likely contribute to the observed, relatively low rates of ESRD.

MATERIALS AND METHODS

We used the Improving Cardiovascular Outcomes in Nova Scotia (ICONS) database that was introduced in October 1997 to study health outcomes, interventions, and resource utilization of consecutive adult ($\geqslant$18 years) patients admitted to hospitals in Nova Scotia, Canada. The ICONS database includes information on patients admitted with a diagnosis of ACS (defined as MI or unstable angina), CHF, or atrial fibrillation. It is a prospective, province-wide, population-based, cohort study of consenting adults. The Capital District Health Authority Research Ethics Board approved the study protocol. Further details of the ICONS study design and methodology have been published.[29]

Inclusion criteria

The study patients were admitted to hospital between 1 October 1997 and 31 October 1999, survived to discharge, and had a discharge diagnosis of ACS or CHF. Each patient

record was unique, and for patients with multiple admissions, the first admission during the time period was used.

Exclusion criteria

Patients discharged with a diagnosis other than ACS or CHF were excluded from the analysis. We did not include the population with atrial fibrillation alone as an independent group, but are looking at that presently. Patients with serum creatinine value missing; less than 40 μmol/l; or greater than 1000 μmol/l; patients with ESRD (defined below) before admission; or who reached ESRD during the index admission were also excluded.

Definitions

We classified patients by discharge diagnosis into the following three mutually exclusive groups: ACS, CHF, or ACS and CHF. We used the MDRD modified formula, based on the admission creatinine, to estimate the GFR in ml/min/1.73 m^2.[30] The coefficient for the Black race was not included in the formula, as race was not documented in the records (The Nova Scotia population is overwhelmingly Caucasian: in the 2001 provincial census, only 1.5% of the population identified themselves as Black or of African origin). We classified renal function into three groups: GFR $\geqslant$60 ml/min/1.73 m^2, GFR 30–$<$60 ml/min/1.73 m^2, and GFR $<$30 ml/min/1.73 m^2. We classified hemoglobin into three groups: $\geqslant$120, 100–$<$120, and $<$100 g/l. We used the diagnosis coded at discharge by medical records personnel (according to the International Classification of Disease, Ninth Revision, Clinical Modification Codes) restricted to 398.9, 410–414, 427.3, 428, 786, and 786.5. We determined the incidence of ESRD by linkage of the ICONS database to the provincial Nova Scotia Department of Heath Medical Service Insurance registry to 31 March 2005, which permitted identification of physician billing codes for transplantation or dialysis. In Nova Scotia, all physician's fees for these services are submitted to the province and recorded in this database. We defined ESRD as treatment with transplantation, peritoneal dialysis, or with treatment by hemodialysis for more than 13 treatments and more than 30 days (Acute peritoneal dialysis is not practiced in Nova Scotia). People who were on hemodialysis for fewer than 30 days at death, or whose death was less than 2 weeks after the last dialysis, were also considered to have ESRD. Patients who were on hemodialysis for fewer than 13 treatments or for fewer than 30 days at the end of the study follow-up period were considered unclassifiable. For patients defined as having ESRD, the date of ESRD was the date of the first dialysis treatment or transplant.

Laboratory testing

We used the admission laboratory data analyzed at the admitting hospitals. No calibration of laboratory creatinine measurement was performed.

Data collection

Trained nurses and health records professionals abstracted baseline variables, laboratory investigations, and discharge medication from the hospital charts. The data were entered into a central ICONS registry database. Patient baseline variables included were age, gender, hypertension (defined as admission blood pressure $\geqslant$140 mm Hg systolic or $\geqslant$90 mm Hg diastolic or a history of hypertension), smoking (current), hyperlipidaemia (defined as total cholesterol $>$6.2 mmol/l or low-density lipoprotein cholesterol $>$2.6 mmol/l, or a history of hyperlipidaemia), and diabetes (defined as random blood glucose $>$11.1 mmol/l or a history of diabetes).

Primary outcome

We determined the primary outcome, ESRD, by linkage of the ICONS database to the provincial Medical Service Insurance registry from 1 October 1995 to 31 March 2005.

Secondary outcomes

We determined mortality by linkage of the ICONS database to the provincial vital statistics registry from 1 October 1997 to 31 March 2005. We determined referral to a nephrologist by linkage of ICONS database with the provincial Medical Service Insurance registry from 1 October 1995 to 31 March 2005 (In Nova Scotia, all visits to a nephrologist result in a physician fee claim being submitted to the provincial government and recorded in this database).

Statistics

We reported baseline patient characteristics as percentages and means (with s.d.) for the three discharge diagnoses groups. We studied the primary ESRD outcome by death-censored unadjusted Kaplan–Meier analysis stratified by discharge diagnoses (a), renal function classified by the MDRD GFR (b), and renal function based on Couchoud creatinine cut-off points of 60 ml/min/1.73 m^2 (104 μmol/l for women and 137 μmol/l for men), and of 30 ml/min/1.73 m^2 (146 μmol/l for women and 177 μmol/l for men) (c). We compared differences between groups (based on discharge diagnosis, GFR class by MDRD GFR, and Couchoud's cut-off points) by log-rank analysis with a value of 0.006 considered significant, based on Bonferonni statistical adjustment of the desired alpha level of 0.05 for nine comparisons.[31]

We used Cox proportional hazards regression modeling to examine the effect of cardiac diagnosis and renal function on the risk of ESRD. Other variables included in the model were age, gender, traditional risk factors (diabetes, hypertension and current smoking), and hemoglobin level. We forced all these variables in the model, regardless of effect size or statistical significance, because of the known prognostic importance of each. We constructed models with and without the variable pre-admission nephrology consultation. We estimated crude hazard rates for death and ESRD using a Poisson distribution. For construction of receiver operating

characteristic curves and for estimation of sensitivity and specificity, in order to avoid problems created by censored observations, we dichotomized patient data into ESRD or no ESRD at 4.44 years (the shortest observed follow-up time). We considered a two-sided *P*-value of less than 0.05 as statistically significant. We performed analyses with SAS V9.1 (SAS Institute, Cary, NC, USA) and SPSS 11.0 (SPSS Inc., Chicago, IL, USA).

DISCLOSURE

All the authors declared no competing interests.

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REFERENCES

1. Sarnak MJ, Levey AS, Schoolwerth AC *et al.* Kidney disease as a risk factor for development of cardiovascular disease. A statement from the American Heart Association Councils on kidney in cardiovascular disease, high blood pressure research, clinical cardiology, and epidemiology and prevention. *Circulation* 2003; **108**: 2154–2169.
2. Parfrey PS. Cardiac disease in dialysis patients: diagnosis, burden of disease, prognosis, risk factors and management. IV. Recommendations for the management of cardiovascular risk factors. *Nephrol Dial Transplant* 2000; **15**(Suppl 5): S58–S68.
3. Smith GL, Lichtman JH, Bracken MB *et al.* Renal impairment and outcomes in heart failure: systematic review and meta-analysis. *J Am Coll Cardiol* 2006; **47**: 1987–1996.
4. Keough-Ryan TM, Kiberd BA, Dipchand CS *et al.* Outcomes of acute coronary syndrome in a large Canadian cohort: impact of chronic renal insufficiency, cardiac interventions, and anemia. *Am J Kidney Dis* 2005; **46**: 845–855.
5. Langston RD, Presley R, Flanders WD *et al.* Renal insufficiency and anemia are independent risk factors for death among patients with acute myocardial infarction. *Kidney Int* 2003; **64**: 1398–1405.
6. Shlipak MG, Heidenreich PA, Noguchi H *et al.* Association of renal insufficiency with treatment and outcomes after myocardial infarction in elderly patients. *Ann Intern Med* 2002; **137**: 555–562.
7. Wright RS, Reeder GS, Herzog CA *et al.* Acute myocardial infarction and renal dysfunction: a high-risk combination. *Ann Intern Med* 2002; **137**: 563–570.
8. Walsh CR, O'Donnell CJ, Camargo CA *et al.* Elevated serum creatinine is associated with 1-year mortality after myocardial infarction. *Am Heart J* 2002; **144**: 1003–1011.
9. Al Suwaidi J, Reddan DN, Williams K *et al.* Prognostic implications of abnormalities in renal function in patients with acute coronary syndromes. *Circulation* 2002; **106**: 974–980.
10. McClellan WM, Langston RD, Presley R. Medicare patients with cardiovascular disease have a high prevalence of chronic kidney disease and a high rate of progression to end-stage renal disease. *J Am Soc Nephrol* 2004; **15**: 1912–1919.
11. Eriksen BO, Ingebretson OC. The progression of chronic kidney disease: a 10-year population-based study of the effects of gender and age. *Kidney Int* 2006; **69**: 375–382.
12. Evans M, Fryzek JP, Elinder C-G *et al.* The natural history of chronic renal failure: results from an unselected, population-based, inception cohort in Sweden. *Am J Kidney Dis* 2005; **46**: 863–870.
13. Fox CS, Larson MG, Leip EP *et al.* Predictors of new-onset kidney disease in a community-based population. *JAMA* 2004; **291**: 844–850.
14. McClellan WM. Epidemiology and risk factors for chronic kidney disease. *Med Clin N Am* 2005; **89**: 419–445.
15. Cody J, Daly C, Campbell M *et al.* Recombinant human erythropoietin for chronic renal failure anaemia in pre-dialysis patients. *Cochrane Database Syst Rev* 2005; **3**: CD003266.
16. Clase CM, Garg AX, Kiberd BA. Classifying kidney problems: can we avoid framing risks as diseases? *Br Med J* 2004; **329**: 912–915.
17. Levey AS, Eckardt K-U, Tsukamoto Y *et al.* Definition and classification of chronic kidney disease: a position statement from Kidney Disease: Improving Global Outcomes (KDIGO). *Kidney Int* 2005; **67**: 2089–2100.
18. Patel UD, Young EW, Ojo AO *et al.* CKD progression and mortality among older patients with diabetes. *Am J Kidney Dis* 2005; **46**: 406–414.
19. Keith DS, Nichols GA, Gullion CM *et al.* Longitudinal follow-up and outcomes among a population with chronic kidney disease in a large managed care organization. *Arch Intern Med* 2004; **164**: 659–663.
20. Go SA, Chertow GM, Fan D *et al.* Chronic kidney disease and the risks of death, cardiovascular disease events, and hospitalization. *N Eng J Med* 2004; **351**: 1296–1305.
21. Hallan SI, Dahl K, Oien CM *et al.* Screening strategies for chronic kidney disease in the general population: follow-up of cross sectional health survey. *Br Med J* 2006; **333**: 1047–1050.
22. Foley RN, Murray AM, Li S *et al.* Chronic kidney disease and the risk for cardiovascular disease, renal replacement, and death in the United States medicare population, 1998 to 1999. *J Am Soc Nephrol* 2005; **16**: 489–495.
23. MacKinnon M, Leenen FH, Ruzicka M. Does ALLHAT change the management of hypertension in chronic kidney disease? *Curr Hypertens Rep* 2005; **7**: 474–483.
24. Rahman M, Pressel S, Davis BR *et al.* Renal outcomes in high-risk hypertensive patients treated with an angiotensin-converting enzyme inhibitor or a calcium channel blocker vs a diuretic. *Arch Intern Med* 2005; **165**: 936–946.
25. Rahman M, Pressel S, Davis BR *et al.* Cardiovascular outcomes in high-risk hypertensive patients stratified by glomerular filtration rate. *Ann Intern Med* 2006; **144**: 172–180.
26. Weiner DE, Tabatabai S, Tighiouart H *et al.* Cardiovascular outcomes and all-cause mortality: exploring the interaction between CKD and cardiovascular disease. *Am J Kidney Dis* 2006; **48**: 392–401.
27. Wattanakit K, Coresh J, Muntner P *et al.* Cardiovascular risk among adults with chronic kidney disease, with or without prior myocardial infarction. *J Am Coll Cardiol* 2006; **48**: 1183–1189.
28. Tonelli M. Should CKD be a coronary heart disease equivalent? *Am J Kidney Dis* 2007; **49**: 8–11.
29. Cox JL On behalf of the ICONS Investigators. Optimizing disease management at a health care system level: the rationale and methods of the improving cardiovascular outcomes in Nova Scotia (ICONS) study. *Can J Cardiol* 1999; **15**: 787–796.
30. Levey AS, Greene T, Kusek JW *et al.* MDRD study group: a simplified equation to predict glomerular filtration rate from serum creatinine. *J Am Soc Nephrol* 2000; **11**: A0828.
31. Couchoud C, Pozet N, Labeeuw M *et al.* Screening early renal failure: cut off values for serum creatinine as an indicator of renal impairment. *Kidney Int* 1999; **55**: 1878–1884.